

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
28 December 2000 (28.12.2000)

PCT

(10) International Publication Number
WO 00/78742 A1

(51) International Patent Classification⁷: C07D 311/68,
405/12, A61K 31/353, A61P 25/00

(21) International Application Number: PCT/GB00/02304

(22) International Filing Date: 14 June 2000 (14.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9914025.3 17 June 1999 (17.06.1999) GB

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ,
PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

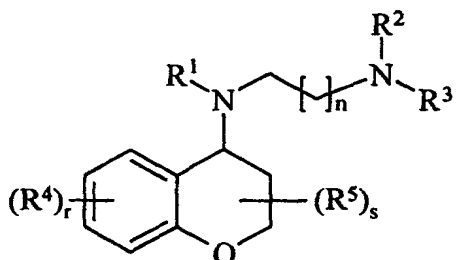
(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CHROMAN DERIVATIVES AGAINST NEUROLOGICAL DISORDERS



(I)

(57) Abstract: Methods for the use of compounds
of formula (I) for treatment of neurological disor-
ders, wherein n, r and s are as defined in the speci-
fication and R¹, R², R³, R⁴ and R⁵ are various sub-
stituents, also as defined in the specification, such
compounds and pharmaceutical compositions con-
taining such compounds.

CHROMAN DERIVATIVES AGAINST NEUROLOGICAL DISORDERS

The present invention relates to chemical compounds, in particular chromans, to processes for their preparation and to chemical intermediates useful in such processes. The present invention further relates to chromans, to pharmaceutical compositions containing them and to their use in methods of therapeutic treatment of animals including man, in particular in the treatment of neurological disorders.

Neurological disorders, for which the present compounds are useful, include stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia. The compounds useful in the present invention act by selectively binding to the [^3H]-emopamil binding site. Compounds with selective action at the [^3H]-emopamil binding site exhibit fewer associated side effects such as hypotension seen with emopamil or behavioural manifestations seen with ifenprodil.

15 **Background**

Emopamil has classically been thought of as a neuroprotective agent whose efficacy is most likely derived from actions at either voltage-sensitive calcium channels (VSCC) or 5-HT₂ receptors. An apparent paradox to this logic is that verapamil, although chemically and pharmacologically very similar to emopamil, is not neuroprotective. While the lack of neuroprotective efficacy by verapamil was initially explained by lack of CNS penetration, recent studies suggest other factors may be involved (Keith et al., Br. J. Pharmacol. 113: 379-384, 1994).

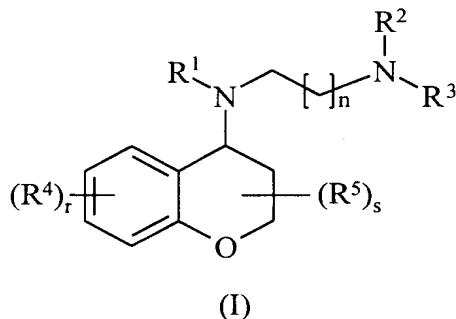
[^3H]-Emopamil binding defines a unique high affinity site that is not related to VSCC, is found in the brain, but is most prevalent in the liver (Moebius et al., Mol. Pharmacol. 43: 139-148, 1993). Moebius et al. have termed this the "anti-ischaemic" binding site on the basis of high affinity displacement by several chemically disparate neuroprotective agents. In liver, the [^3H]-emopamil binding site is localised to the endoplasmic reticulum.

Neuroprotective compounds are known, for example emopamil and ifenprodil, that exhibit high affinity for the [^3H]-emopamil binding site. However these are not selective inhibitors and exhibit activity either at neuronal VSCC, the polyamine site of the NMDA receptor (N-Methyl-D-aspartate) and/or the sigma-1 binding site.

Summary of the Invention

In one aspect of the present invention a new method for using compounds having selective action at the [³H]-emopamil binding site and that are neuroprotective without acting directly at either VSCC or NMDA receptors is disclosed.

- 5 Compounds of the invention that have selective action at the [³H]-emopamil binding site are compounds of formula (I):



wherein:

- 10 R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;
 R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring, wherein said C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6} alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, N - C_{1-6} alkylamino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkoxycarbonyl, N - C_{1-6} alkylcarbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl)₂amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl)₂carbamoyl, C_{1-6} alkylS(O)_a wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl)₂sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl or phenyl C_{1-6} alkyl;

or R² and R³ and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, N-(C₁₋₆alkyl)amino, N,N-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, N-(C₁₋₆alkyl)carbamoyl, N,N-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0, 1 or 2, C₁₋₆alkoxycarbonyl, N-(C₁₋₆alkyl)sulphamoyl, N,N-(C₁₋₆alkyl)₂sulphamoyl or phenylC₁₋₆alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkanoyl or C₁₋₆alkylsulphonyl;

R⁴ at each occurrence is selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkyl, cyano, nitro or C₂₋₆alkenyl;

R⁵ is C₁₋₆alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R⁴ may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the value of R⁵ may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In another aspect of the present invention, new pharmaceutical compositions containing compounds of formula (I), or *in vivo*-hydrolysable esters, amides or carbamates thereof, together with a pharmaceutically-acceptable carrier such as an excipient, diluent or stabilizer or combinations thereof as further defined herein are disclosed.

In a further aspect of the present invention, the use of a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in the manufacture of a medicament for use in the inhibition of the [³H]-emopamil binding site in a warm-blooded animal is disclosed.

In yet a further aspect of the present invention, novel compounds are disclosed which are compounds of formula (I) with a proviso wherein in such compounds:

if r is 1, R⁴ is a 6-linked cyano moiety, s is 2 and both R⁵ moieties are 2-linked methyl, n is 1, and R¹ and R² are both H, then R³ is not phenyl or benzyl;

if r and s are both 0, R^1 is H and n is 2, then R^1 and R^2 are not both ethyl or not both H, or
if r and s are both 0, R^1 is H and n is 1, then R^1 and R^2 are not both ethyl.

Detailed Description of the Invention

In this specification the term “alkyl” includes both straight and branched chain alkyl
5 groups but references to individual alkyl groups such as “propyl” are specific for the straight
chain version only. A similar convention applies to “alkenyl”, “alkynyl” and other radicals,
for example “phenylC₁₋₆alkyl” includes 2-phenylethyl, 2-phenylpropyl and 3-phenylpropyl.
The term “halo” refers to fluoro, chloro, bromo and iodo.

The term aryl refers to an unsaturated carbon ring. Preferably aryl is phenyl,
10 naphthyl or biphenyl. More preferably aryl is phenyl.

The term “heteroaryl” or “heteroaryl ring” refers to, unless otherwise further
specified, a monocyclic-, bicyclic- or tricyclic-, 5- to 14-membered ring that is unsaturated or
partially unsaturated, with up to five ring heteroatoms selected from nitrogen, oxygen and
sulphur wherein a -CH₂- group can optionally be replaced by a -C(O)-, and a ring nitrogen
15 atom may be optionally oxidised to form the N-oxide. Examples of such heteroaryls include
thienyl, furyl, pyranal, pyrrolal, imidazolal, pyrazolal, thiazolal, oxazolal, isoxazolal, pyridal,
pyridal-*N*-oxide, oxopyridal, oxoquinolal, pyrimidinyl, pyrazinyl, oxopyrazinyl, pyridazinyl,
indolinyl, benzofuranyl, benzimidazolal, benzothiazolal, quinolal, isoquinolinyl, quinazolinyl,
xanthenyl, quinoxalinyl, indazolal, benzofuranyl and cinnolinyl.

The term “heterocyclal” or “heterocyclic ring” refers to, unless otherwise further
specified, a mono- or bicyclic-, 5- to 14-membered ring, that is totally saturated, with up to
five ring heteroatoms selected from nitrogen, oxygen and sulphur wherein a -CH₂- group can
optionally be replaced by a -C(O)-. Examples of such heterocyclals include morpholinyl,
pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, homopiperidinyl,
25 homopiperazinyl and quinuclidinyl.

Where optional substituents are chosen from “one or more” groups it is to be
understood that this definition includes all substituents being chosen from one of the specified
groups or the substituents being chosen from two or more of the specified groups.

In the present invention, examples of C₁₋₆alkyl include C₁₋₄alkyl such as methyl,
30 ethyl, isopropyl and *t*-butyl;
examples of phenylC₁₋₆alkyl include phenylC₂₋₆alkyl such as phenylC₁₋₄alkyl such as phenylC₂₋₄
alkyl such as benzyl, phenylethyl and phenylpropyl;

examples of C₁₋₆alkoxycarbonyl include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl;

examples of C₁₋₆alkoxy include methoxy, ethoxy and propoxy;

examples of C₁₋₆alkanoylamino include formamido, acetamido and propionylamino;

- 5 examples of C₁₋₆alkylS(O)_a where a is 0, 1 or 2 include C₁₋₆alkylsulphonyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl;

examples of C₁₋₆alkylsulphonyl include mesyl and ethylsulphonyl;

examples of C₁₋₆alkanoyl include propionyl and acetyl;

examples of *N*-C₁₋₆alkylamino include *N*-methylanino and *N*-ethylanino;

- 10 examples of *N,N*-(C₁₋₆alkyl)₂amino include *N,N*-dimethylanino, *N,N*-diethylanino and *N*-ethyl-*N*-methylanino;

examples of C₃₋₁₂cycloalkyl include cyclopropyl and cyclohexyl;

examples of C₃₋₁₂cycloalkyl fused to a benzene ring are 1,2,3,4-tetrahydronaphthyl and 2,3-dihydroindenyl;

- 15 examples of C₂₋₆alkenyl include vinyl, allyl and 1-propenyl;

examples of C₂₋₆alkynyl include ethynyl, 1-propynyl and 2-propynyl;

examples of haloC₂₋₆alkyl include 2-chloroethyl and 2-bromopropyl;

examples of *N*-(C₁₋₆alkyl)sulphamoyl include *N*-methylsulphamoyl and *N*-ethylsulphamoyl;

examples of *N,N*-(C₁₋₆alkyl)₂sulphamoyl include *N,N*-dimethylsulphamoyl and *N*-methyl-*N*-

- 20 ethylsulphamoyl;

examples of *N*-(C₁₋₆alkyl)carbamoyl include *N*-methylcarbamoyl and *N*-ethylcarbamoyl;

examples of *N,N*-(C₁₋₆alkyl)₂carbamoyl include *N,N*-dimethylcarbamoyl and *N*-methyl-*N*-ethylcarbamoyl, and

examples of C₁₋₆alkanoyloxy include propionyloxy, acetyloxy and formyloxy.

- 25 Preferably R¹ is hydrogen or C₁₋₆alkyl

More preferably R¹ is hydrogen or C₁₋₄alkyl.

Particularly R¹ is hydrogen or methyl.

More particularly R¹ is methyl.

- In one aspect of the invention, preferably R² and R³ are independently selected from
 30 hydrogen, C₁₋₆alkyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C₃₋₁₂cycloalkyl and C₃₋₁₂cycloalkyl fused to a benzene ring; wherein said C₁₋₆alkyl, is optionally substituted with one or more groups selected from halo, nitro, hydroxy, C₁₋₆alkoxy, cyano,

amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, *N*-C₁₋₆alkylamino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkoxycarbonyl, *N*-C₁₋₆alkylcarbamoyl or *N,N*-(C₁₋₆alkyl)₂carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C₃₋₁₂cycloalkyl or C₃₋₁₂cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl or heterocycle may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0, 1 or 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl and phenylC₁₋₆alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl or phenylC₁₋₆alkyl.

In another aspect of the invention preferably R² and R³ and the nitrogen atom to which they are attached in combination form a ring selected from 1,2,3,4-tetrahydroisoquinolinyl, morpholinyl, piperidinyl, pyrrolidinyl, homopiperidinyl and wherein said ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0, 1 or 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl or phenylC₁₋₆alkyl.

In a further aspect of the invention, preferably R² and R³ are independently selected from hydrogen, aryl and C₁₋₆alkyl optionally substituted with aryl; or R² and R³ and the nitrogen atom to which they are attached in combination form a heterocyclic ring.

More preferably R² and R³ are independently selected from methyl, ethyl or benzyl, or R² and R³ and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl, piperidin-1-yl or morpholino ring.

Particularly R² and R³ are independently selected from methyl or benzyl, or R² and R³ and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl or piperidin-1-yl ring.

Preferably r is 0.

Preferably s is 0.

In one aspect of the invention preferably n is 1.

In another aspect of the invention preferably n is 2.

5 Therefore in a preferred aspect of the invention there is provided an compound of formula (I) as depicted above wherein:

R¹ is hydrogen or C₁₋₆alkyl;

R² and R³ are independently selected from hydrogen, aryl and C₁₋₆alkyl optionally substituted with aryl;

10 or R² and R³ and the nitrogen atom to which they are attached in combination form a heterocyclic ring;

r is 0;

s is 0;

n is 1 or 2;

15 or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a more preferred aspect of the invention there is provided a compound of the formula (I) as depicted above wherein:

R¹ is hydrogen or methyl;

20 R² and R³ are independently selected from methyl, ethyl or benzyl;

or R² and R³ and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl, piperidin-1-yl or morpholino ring;

r is 0;

s is 0;

25 n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

In a particular aspect of the invention there is provided a compound of formula (I) as depicted above wherein:

30 R¹ is hydrogen or methyl;

R² and R³ are independently selected from methyl or benzyl,

or R² and R³ and the nitrogen atom to which they are attached in combination form a pyrrolidin-1-yl or piperidin-1-yl ring;

r is 0;

s is 0;

5 n is 1 or 2;

or a pharmaceutically-acceptable salt or and *in vivo*-hydrolysable ester, amide or carbamate thereof.

Preferred compounds of the invention are those of Examples.

A preferred aspect of the invention relates to any one of the Examples.

10 Preferred aspects of the invention relate to a compound according to formula (I) or a pharmaceutically-acceptable salt thereof.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an
15 alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or amino acids for example lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred
20 pharmaceutically-acceptable salt is a sodium salt.

The compounds of formula (I) possess a chiral centre at the 4-position of the chroman ring. Certain compounds of formula (I) may also have other chiral centres, for example certain of the values of R², R³, R⁴, R⁵ and certain of the optional substituents may possess chiral centres. It is to be understood that the invention encompasses all such optical
25 isomers and diastereoisomers of compounds of formula (I) that inhibit the [³H]-emopamil binding site.

The invention further relates to all tautomeric forms of the compounds of formula (I).

It is also to be understood that certain compounds of the formula (I) can exist in
30 solvated as well as unsolvated forms such as, for example, hydrated forms and that the invention encompasses all such solvated and unsolvated forms.

In vivo-hydrolysable esters, amides and carbamates are compounds that hydrolyse in the human body to produce the parent compound. Such esters, amides and carbamates can be identified by administering, for example intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids. Suitable *in vivo*-hydrolysable amides and carbamates include N-carbomethoxy and N-acetyl.

An *in vivo*-hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically-acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

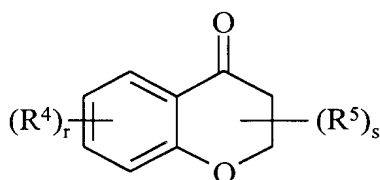
Suitable pharmaceutically-acceptable esters for carboxy include C₁₋₆alkoxymethyl esters for example methoxymethyl, C₁₋₆alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C₃₋₈cycloalkoxy-carbonyloxyC₁₋₆alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C₁₋₆alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo*-hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α -acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo*-hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof which process (wherein R¹, R², R³, R⁴, R⁵, n, r and s are, unless otherwise specified, as defined in formula (I)) comprises of:

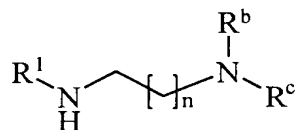
- a) reacting a ketone of formula (II):

-10-



(II)

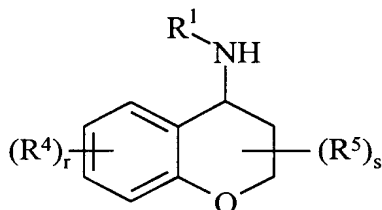
with an amine of formula (III):



(III);

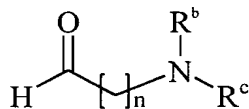
wherein R^b and R^c are R^2 and R^3 respectively, unless the value of R^2 and/or R^3 is hydrogen, in which case the appropriate R^b and/or R^c is a suitable amino protecting group such as those defined below; or

b) reacting an amine of formula (IV):



(IV)

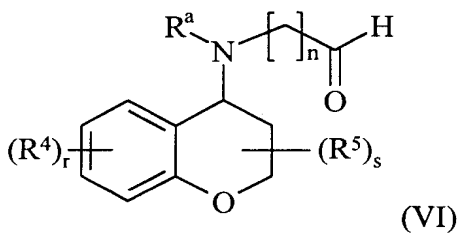
with an aldehyde of formula (V):



(V)

15 wherein R^b and R^c are as defined above; or

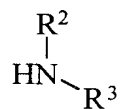
c) reacting an aldehyde of formula (VI):



(VI)

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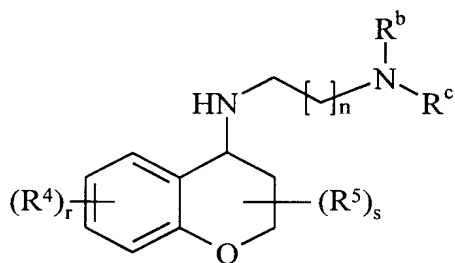
with an amine of formula:



(VII)

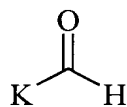
wherein R^a is R^1 unless the value of R^1 is hydrogen, in which case R^a is a suitable amino protecting group such as those defined below; or

d) if R^1 is C_{1-6} alkyl, reacting a compound of formula (VIII):



(VIII)

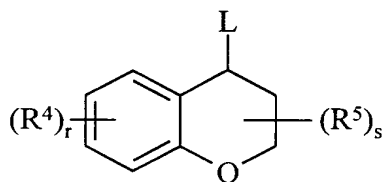
wherein R^b and R^c are as defined above, with a compound of formula (IX);



(IX)

wherein K is hydrogen or C_{1-5} alkyl; or

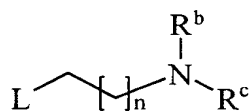
e) reacting a compound of formula (X):



(X)

wherein L is a suitable displaceable group, with an amine of formula (III); or

f) reacting an amine of formula (IV) with a compound of formula (XI):

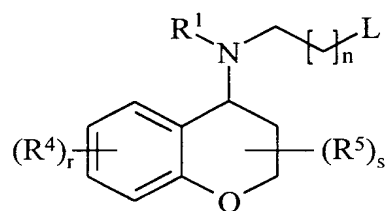


(XI)

-12-

wherein L is a suitable displaceable group and R^b and R^c are as defined above; or

g) reacting a compound of formula (XII):



(XII)

5 wherein L is a suitable displaceable group, with an amine of formula (VII); or

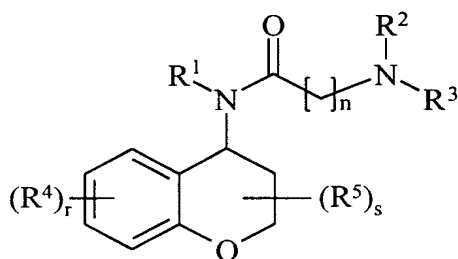
h) if R¹ is not hydrogen, reacting a compound of formula (VIII) with a compound of formula (XIII):



(XIII)

10 wherein L is a suitable displaceable group;

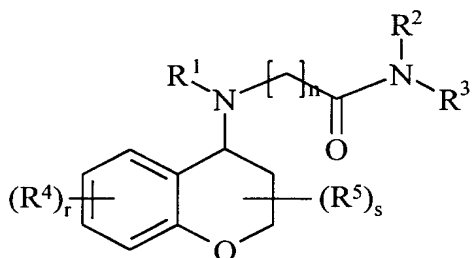
i) reducing a compound of formula (XIV):



(XIV)

or

15 j) reducing a compound of formula (XV):

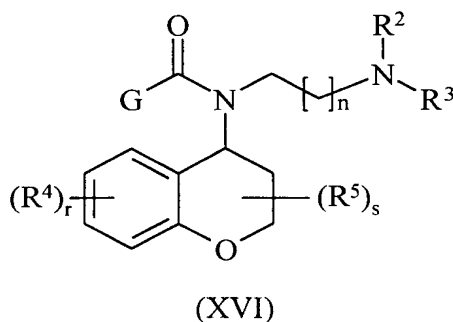


(XV)

or

k) if R¹ is not hydrogen, reducing a compound of formula (XVI):

-13-



wherein:

1) for preparing a compound wherein R^1 is methyl, G is a suitable displaceable group; or

5 2) for preparing a compound wherein R^1 is C_{2-6} alkyl, G is C_{1-5} alkyl;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups; or

iii) forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or

10 carbamate.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

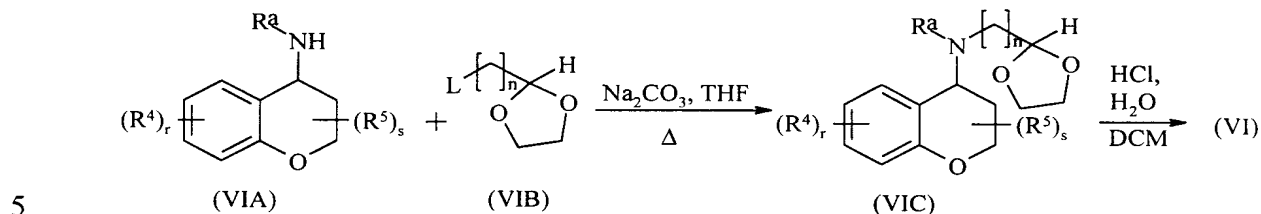
When G is a suitable displaceable group, suitable values for G are C_{1-6} alkoxy, for
15 example methoxy or ethoxy.

Specific reaction conditions for the above reactions a), b), c) and d) are as follows:

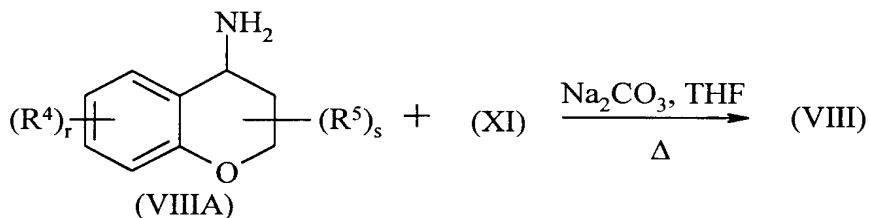
Ketones or aldehydes may be reacted with amines under standard reductive amination conditions. Imine formation may optionally be assisted with a Lewis acid for example titanium tetrachloride, in an inert solvent for example toluene. The reduction may
20 occur for example in the presence of a reducing agent such as hydrogen and a hydrogenation catalyst (for example palladium on carbon), or zinc and hydrochloric acid, or sodium cyanoborohydride, or sodium triacetoxyborohydride, or sodium borohydride, iron pentacarbonyl and alcoholic potassium hydroxide, or borane and pyridine or formic acid. The reaction is preferable carried out in the presence of a suitable solvent such as an alcohol, for
25 example methanol or ethanol, and at a temperature in the range of 0-50 °C, preferably at or near room temperature.

Compounds of formula (II), (III), (IV), (V), (VII) and (IX) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Compounds of formula (VI) may be prepared according to the following scheme:



Compounds of formula (VIII) may be prepared according to the following scheme:



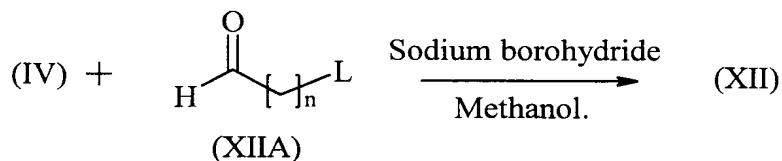
10 Compounds of formula (VIA), (VIB) and (VIII A) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Specific reaction conditions for the above reactions e), f), g) and h) are as follows:

15 Amines and compounds with suitable leaving groups are reacted together under standard alkylation conditions. For example in the presence of a base, such as an inorganic base for example sodium carbonate or sodium hydroxide or in the presence of excess amine, in the presence of an inert solvent for example tetrahydrofuran, acetonitrile or toluene and at a temperature in the range of 50-120 °C, preferably at or near reflux.

Compounds of formula (X), (XI) and (XIII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

20 Compounds of formula (XII) may be prepared according to the following scheme.

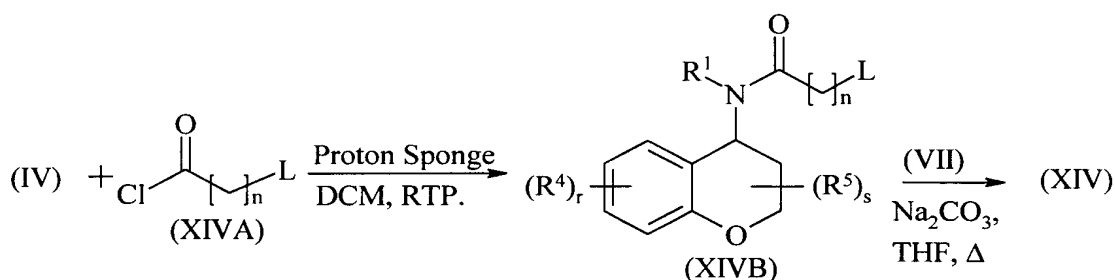


Compounds of formula (XIIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

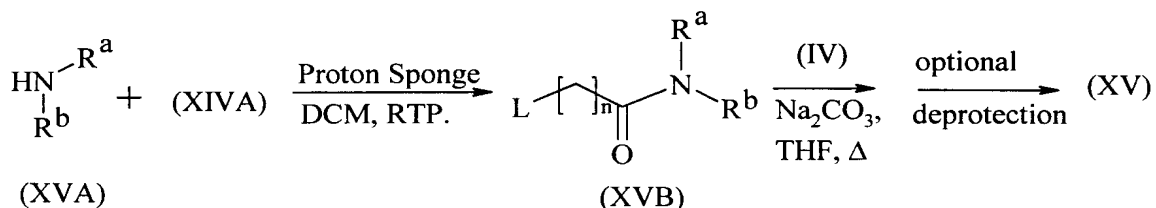
Specific reaction conditions for the above reactions i), j) and k) are as follows:

Compounds of formula (XIV), (XV) and (XVI) are reduced under standard reduction conditions for reducing an amide to an amine. For example, in the presence of a reducing agent such as borane, sodium borohydride or lithium aluminium hydride, in an inert solvent such as toluene or tetrahydrofuran, and at a temperature in the range of 50-120 °C, preferably at or near reflux.

Compounds of formula (XIV) may be prepared according to the following scheme:

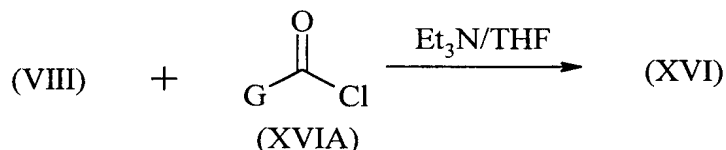


Compounds of formula (XV) may be prepared according to the following scheme:



wherein R^a, R^b and L are as hereinbefore defined.

Compounds of formula (XVI) may be prepared according to the following schemes:



Compounds of formula (XIVA) and (XVIA) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

When an optically active form of a compound of the formula (I) is required, it may be obtained, for example, by carrying out one of the aforesaid procedures using an optically

active starting material or by resolution of a racemic form of said compound using a conventional procedure.

An example of converting one compound of formula (I) into another compound of formula (I) is the conversion of R^1 , R^2 or R^3 when they are hydrogen to a different R^1 , R^2 , or R^3 . For example an alkyl group could be introduced by standard alkylation or reductive
5 amination techniques, such as those described above.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately
10 following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution
15 reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications
20 include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where
25 protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

30 A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an

arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed for example, by hydrolysis with a
5 suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon,
10 or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for
15 example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide.
20 Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may
25 be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

30 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (I). To use compounds of formula (I) or a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or carbamate

thereof for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The pharmaceutical compositions of compounds of this invention may be
5 administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided
10 powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions. A preferred route of administration is intravenously in sterile isotonic solution.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or
15 sequentially) with, one or more pharmacological agents of value in treating one or more disease conditions referred to hereinabove.

The pharmaceutical compositions of this invention will normally be administered to humans so that, for example, a daily dose of 0.05 to 75 mg/kg body weight (and preferably of 0.1 to 30 mg/kg body weight) is received. This daily dose may be given in divided doses as
20 necessary, the precise amount of the compound received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention in association with a pharmaceutically-acceptable excipient or carrier.

25 According to a further aspect of the present invention there is provided a compound of the formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

A further feature of the present invention is a compound of formula (I) and
30 pharmaceutically-acceptable salts or an *in vivo*-hydrolysable ester, amide or carbamate thereof, for use as a medicament to inhibit the [³H]-emopamil binding site in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, in the manufacture of a medicament for use in the inhibition of the [³H]-emopamil binding site in a warm-blooded animal such as a human being.

According to a further feature of the invention there is provided a method of inhibiting of the [³H]-emopamil binding site in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I) or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof, as defined hereinbefore.

The following Biological Test Methods, Data and Examples serve to illustrate the present invention.

Biological Test Methods

³H-Emopamil binding to guinea pig liver membranes

The method of (-)-³H-emopamil binding was a modification of Zech, C., Staudinger R., Mühlbacher, J. and Glossmann, H. Novel sites for phenylalkylamines: characterisation of a sodium-sensitive drug receptor with (-)-³H-emopamil. Eur. J. Pharm. **208**: 119-130, 1991. The reaction mixture contained:

Assay buffer: 10 mM Tris-HCl, 0.1 mM phenylmethylsulfonyl fluoride (PMSF), 0.2% bovine serum albumin (BSA), pH 7.4 at 4 °C.

Radioligand: 0.96 nM (-)-³H-emopamil (Amersham).

Guinea pig liver membranes: 40mg/mL original wet weight.

Compounds: 1-300 nM.

Total volume: 500 µL.

This mixture was incubated for 60 minutes at 37 °C. The incubation was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenimine (PEI) and washed three times with 5 mL of wash buffer containing 10 mM Tris-HCl, 10 mM MgCl₂, 0.2% BSA, pH 7.4 at 25 °C. Specific binding was defined with 10 µM emopamil. In general compounds with an IC₅₀ below 300nM in this test were of interest.

Guinea-pig liver membrane preparation:

Male guinea pigs were sacrificed by CO₂ asphyxiation with dry ice. The livers were

quickly excised and weighed and rinsed in membrane preparation buffer containing 10 mM Hepes, 1 mM Tris base-EDTA, 250 mM sucrose, pH 7.4. The livers were then minced, homogenised in 10 times volume with a motor driven Teflon-glass homogeniser with three strokes on ice. The homogenate was centrifuged at 1000 x g in a SS34 rotor for 5 minutes at 4 °C. The supernatant was filtered through 4 layers of gauze and then centrifuged at 8000 x g for 10 minutes at 4 °C. This resulting supernatant was centrifuged at 40,000 x g for 15 minutes at 4 °C. The resulting pellet was resuspended in assay buffer and centrifuged again at 40,000 x g for 15 minutes at 4 °C. This pellet was resuspended in assay buffer (2.5 fold with respect to original wet weight) and homogenised with one stroke with the Teflon-glass homogeniser. Aliquots of 1 mL were stored at -70 °C.

³H-D-888 binding to rat brain cortical membranes

The method of ³H-D-888 binding was a modification of Reynolds, I.J., Snowman, A.M. and Synder, S.H. (-)-[³H] Desmethoxyverapamil labels multiple calcium channel modular receptors in brain and skeletal muscle membranes: differentiation by temperature and dihydropyridines. J. Pharmacol. Exp. Ther. **237**: no.3, 731-738, 1986.

The assay tubes contained the following:

assay buffer: 50 mM Hepes, 0.2% BSA, pH 7.4

radioligand: 1 nM ³H-D888 (Amersham)

rat cortical membranes: 6 mg/mL original wet weight

compounds: 0.3-100 µM

Total volume: 1000 µl

This mixture was incubated for 60 minutes at 25 °C. The assay was terminated by filtering with a Brandel Cell Harvester over Whatman GF/C filters that had been soaked for at least 120 minutes in 0.3% polyethylenamine (PEI) and washed three times with 5 mL of wash buffer containing 20 mM Hepes, 20 mM MgCl₂, pH 7.4. Specific binding was measured with 10 µM methoxyverapamil (D-600). This assay was used to determine in vitro selectivity of compounds vs. L-type voltage sensitive calcium channels, i.e. high affinity for the ³H-D888 binding site would show a lack of selectivity.

Rat brain cortical membrane preparation

Male Sprague-Dawley Rats were sacrificed by decapitation and the brains were quickly excised. The cerebellum and brain stem were removed and discarded; and the rest of

the brain was rinsed in 320 mM sucrose. The brain was then homogenised in a 10-fold volume of 320 mM sucrose with a motor driven Teflon-glass homogeniser using 10 strokes on ice. The homogenate was spun at 1000 x g for 10 minutes at 4 °C in a SS-34 rotor. The supernatant was then spun at 29,000 x g for 20 minutes. The resulting pellet was resuspended
5 in membrane buffer (5 mM Hepes, 0.2% BSA, pH 7.4) to a final concentration of 60 mg original wet weight/ mL.

Gerbil Global Model of Cerebral Ischaemia

Male Mongolian gerbils (Charles River) weighing 60-70 grams are used in these experiments. They are housed in individual cages with food (Purina Rodent Chow) and water
10 available *ad libitum*. The animal room is maintained at 23 ± 2 °C, and is on an automatic 12 hour light cycle.

The gerbils are brought to the surgical suite and dosed intraperitoneally with the test agent or vehicle, forty five minutes prior to surgery. Drugs are administered at a volume of 5 mL/kg (intraperitoneal). Vehicle is generally saline, with sodium phosphate added to adjust
15 pH, if needed. Forty-five minutes after dosing the gerbils are anaesthetised with halothane (3.3%) which is delivered along with oxygen (1.5 l/M) through a face mask. After the gerbils are anaesthetised, halothane is continued at a maintenance level of 1.5-2% along with oxygen. The ventral surface of the neck is shaved and cleaned with alcohol. Surgical procedures are carried out on a thermostat-controlled heating pad set to 37 °C. An incision is made in the
20 neck, the carotid arteries are dissected away from the surrounding tissue, and isolated with a 5 cm length of Silastic tubing. When both arteries have been isolated they are clamped with microaneurysm clips (Roboz Instruments). The arteries are visually inspected to determine that the blood flow has been stopped. After 5 minutes the clips are gently removed from the arteries and blood flow begins again. A sham control group is treated identically but is not
25 subjected to carotid artery occlusion. The incisions are closed with suture and the gerbils removed from the anaesthesia masks and placed on another heating pad to recover from the anaesthesia. When they have regained the righting reflex and are beginning to walk around, they are again dosed with the test compound and returned to their home cages. This occurs approximately five minutes after the end of surgery.

30 Twenty-four hours post ischaemia gerbils are tested for spontaneous locomotor activity, using a Photobeam Activity System from San Diego Instruments. They are individually placed in Plexiglas chambers measuring 27.5 cm x 27.5 cm x 15 cm deep. The

chambers are surrounded by photocells, and every time a beam is broken one count is recorded. Each gerbil is tested for two hours, and cumulative counts are recorded at 30, 60, 90, and 120 minutes. Mean counts are recorded for each group and drug groups are compared to control with an ANOVA and Bonferroni post test. After each gerbil is tested it is returned
5 to its home cage. At this time gerbils are also observed for any changes from normal behaviour.

For the next two days no specific testing is performed, but the gerbils are observed two to three times per day for any unusual behaviours or obvious neurological symptoms (i.e. ataxia, convulsions, stereotypic behaviour). Four days post ischaemia the gerbils are sacrificed
10 by decapitation and their brains removed and preserved in 10% buffered formalin. Brains were removed, fixed and stained with hematoxylin and eosin. Under a light microscope, hippocampal fields were observed and graded for damage to the CA1 subfield: 0 to 4 scale, with 0 representing no damage and 4 representing extensive damage.

Transient Focal Ischaemia in Rats

15 The method was as described by Lin, T-N., He, Y.Y., Wu, G., Khan, M. And Hsu, C.Y. Effect of brain edema on infarct volume in a focal model cerebral ischaemia model in rats. Stroke **24**:117-121, 1993, which model is considered to be relevant to the clinical situation. Male Long-Evans rats 250-350 g were used. Surgery leading to focal ischaemia was conducted under anaesthesia with 100 mg/kg ketamine and 5 mg/kg i.m. xylazine. Rectal
20 temperature was monitored and maintained at 37.0 ± 0.5 °C. The right middle cerebral artery (MCA) was exposed using microsurgical techniques. The MCA trunk was ligated immediately above the rhinal fissure with 10-0 suture. Complete interruption of blood flow was confirmed under an operating microscope. Both common carotid arteries were then occluded using nontraumatic aneurysm clips. After a predetermined duration of ischaemia (45
25 min), blood flow was restored in all three arteries. Twenty-four hours post occlusion, rats were killed under ketamine anesthesia by intracardiac perfusion with 200 mL of 0.9% NaCl. The brain was removed and processed with 2% triphenyltetrazolium chloride to identify and quantitate the infarcted brain region. Compounds were administered by intravenous infusion for 4 hours.

Data

The following results were obtained in the ³H-Emopamil binding to guinea pig liver membranes test.

| Example | IC ₅₀ (nM) |
|---------|-----------------------|
| 1 | 175.5 |
| 4 | 68 |
| 7 | 268 |

Examples

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated:-

- 5 (i) concentrations were carried out by rotary evaporation *in vacuo*;
- (ii) operations were carried out at ambient temperature, that is in the range 18-26 °C and under a nitrogen atmosphere otherwise stated;
- (iii) column chromatography (by the flash procedure) was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;
- 10 (iv) yields are given for illustration only and are not necessarily the maximum attainable;
- (v) the structure of the end-products of the formula I were generally confirmed by NMR and mass spectral techniques - proton magnetic resonance spectra were determined in DMSO- δ_6 unless otherwise stated using a Varian Gemini 2000 spectrometer operating at a field strength of 300 MHz; chemical shifts are reported in parts per million downfield from
- 15 tetramethylsilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; bs, broad singlet; d, doublet; AB or dd, doublet of doublets; t, triplet, dt, double of triplets, m, multiplet; bm, broad multiplet and unless otherwise stated ¹H NMR is quoted; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data
- 20 or negative ion data were collected, in this application, (M+H)⁺ is quoted unless otherwise stated;
- (vi) intermediates were not generally fully characterised and purity was in general assessed mass spectral (MS) or NMR analysis; and
- (vii) in which the following abbreviations (also used hereinabove) may be used :-
- 25 DMSO is dimethylsulphoxide;
- m/s is mass spectroscopy;
- THF is tetrahydrofuran;

DCM is dichloromethane;
Com Av is commercially available; and
SM is starting material.

5 **Example 1**

Chroman-4-yl-(2-piperidin-1-ylethyl)amine

4-Chromanone (0.960 g, 6.48×10^{-3} mole) and 1-(2-aminoethyl)piperidine (5.163 g, 4.03×10^{-2} mole) were combined in toluene (20 mL) and cooled to 0 °C (ice/water/sodium chloride). The mixture was treated with titanium tetrachloride solution (1.0 M in toluene, 3.2 mL, 3.20×10^{-3} mole), maintaining the reaction temperature at <5 °C. Upon complete addition, the cooling bath was removed and the mixture stirred at ambient temperature for 24.5 hours. The solid was removed by vacuum filtration and the filtrate concentrated to a yellow oil. A solution of the oil in methanol (15 mL) was treated with sodium borohydride (0.253 g, 6.69×10^{-3} mole) and stirred at ambient temperature for 30 minutes. The solvent was evaporated and the residue partitioned between water and diethyl ether. The aqueous portion was extracted with additional diethyl ether. The combined extracts were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1% NH₄OH:5% MeOH:94% DCM (v/v/v), to give the product as a pale yellow oil (1.15 g, 68%). NMR: 1.27-1.60 (m, 6H), 1.72-1.98 (m, 3H), 2.20-2.45 (m, 6H), 2.57-2.80 (m, 2H), 3.68 (t, 1H), 4.07-4.29 (m, 2H), 6.73 (d, 1H), 6.84 (t, 1H), 7.11 (t, 1H), 7.23 (d, 1H). m/s: 261.

Example 2

Chroman-4-yl-(N-methyl-2-piperidin-1-ylethyl)amine

4-[2-(Piperidin-1-yl)ethylamino]chroman (Example 1) (0.700 g, 2.69×10^{-3} mole) was dissolved in methanol (16 mL) and treated with formaldehyde (37% aqueous, 5.4 mL, 7.20×10^{-2} mole). After two hours, sodium borohydride (0.975 g, 2.58×10^{-2} mole) was added and the mixture was stirred at ambient temperature for 38 hours. The reaction mixture was evaporated and the residue partitioned between water and diethyl ether. The aqueous portion was extracted with additional diethyl ether. The combined organic portions were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1% NH₄OH:5% MeOH:94% CH₂Cl₂ (v/v/v), to give the product as a colourless oil (0.175 g, 24%). NMR: 1.23-1.57 (m, 6H), 1.80-2.03 (m, 2H), 2.10-2.60 (m, 11H), 3.92-

4.15 (m, 2H), 4.23-4.36 (m, 1H), 6.70 (d, 1H), 6.85 (t, 1H), 7.05 (t, 1H), 7.44 (d, 1H). m/s: 274.

Example 3

(S)-Chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]amine

- 5 (a) A suspension of *N*-(*t*-butoxycarbonyl)glycine (2.44 g, 1.39×10^{-2} mole) and 1-hydroxybenzotriazole (1.80 g, 1.33×10^{-2} mole) in DCM (50 mL) was treated with 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3.13 g, 1.63×10^{-2} mole) and triethylamine (2.4 mL, 1.72×10^{-2} mole), respectively. Immediately, a solution of (*S*)-4-aminochroman (2.00 g, 1.34×10^{-2} mole) in DCM (30 mL) was added. After stirring at
10 ambient temperature for 19 hours, the reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to an oil (4.17 g, 100%). ¹H NMR (DMSO): 1.39 (s, 9H), 1.80-2.08 (m, 2H), 3.44-3.61 (m, 2H), 4.11-4.26 (m, 2H), 4.94-5.05 (m, 1H), 6.77 (d, 1H), 6.81-7.00 (m, 2H), 7.08-7.20 (m, 2H), 8.24 (d, 1H). m/s: 307.
- 15 (b) The oil from step (a) (4.17 g, 1.36×10^{-2} mole) in THF (70 mL) was treated with concentrated hydrochloric acid (2 mL) and heated at 60 °C for two hours. Additional concentrated hydrochloric acid (2 mL) was added and heating continued at 60 °C for two hours. The reaction mixture was partitioned between 1N sodium hydroxide solution and DCM. The aqueous portion was extracted with additional DCM. The combined organic
20 portions were washed (water, brine), dried, and evaporated to a white solid. The solid was dissolved in DCM and purified by chromatography, eluting with 10% 2.0 M ammonia in methanol:90% DCM (v/v), to give the product as a white solid (2.50 g, 89%). ¹H NMR (DMSO): 1.82-2.20 (m, 4H), 3.13 (s, 2H), 4.09-4.27 (m, 2H), 4.95-5.06 (m, 1H), 6.77 (d, 1H), 6.82-6.92 (m, 1H), 7.07-7.22 (m, 2H), 8.17 (d, 1H).
- 25 (c) A suspension of the white solid from step (b) (2.50 g, 1.21×10^{-2} mole) and sodium carbonate (3.86 g, 3.64×10^{-2} mole) in THF (62 mL) was treated with α,α' -dibromo-*o*-xylene (3.19 g, 1.21×10^{-2} mole) followed by refluxing for six hours. The reaction mixture was partitioned between water and DCM. The aqueous portion was extracted with additional DCM. The combined organic portions were washed (water, brine), dried, and evaporated to a
30 white solid. The solid was dissolved in DCM/methanol and purified by chromatography, eluting with 5% 2.0M ammonia in methanol:95% DCM (v/v), to give the product as a white solid (3.51 g, 94%). ¹H NMR (DMSO): 1.92-2.08 (m, 2H), 3.42 (s, 2H), 4.00 (s, 4H), 4.16-

4.25 (m, 2H), 5.01-5.13 (m, 1H), 6.76 (d, 1H), 6.83-6.94 (m, 1H), 7.08-7.28 (m, 6H), 8.31 (d, 1H). m/s: 309.

(d) A suspension of the white solid from step (c) (3.51 g, 1.14×10^{-2} mole) in THF (115 mL) was treated with lithium aluminum hydride (1.76 g, 4.64×10^{-2} mole) and
5 refluxed for two hours. The reaction mixture was quenched with sodium sulfate decahydrate until effervescence ceased. Additional THF and diethyl ether were added to aid stirring. The reaction mixture was filtered through diatomaceous earth and the filtrate evaporated to pink oil which was purified by chromatography, eluting with 5% 2.0M ammonia in methanol:95% DCM (v/v), to give the product as a tan oil (2.49 g, 74%). ^1H NMR (DMSO): 1.83-2.30 (m,
10 3H), 2.67-2.91 (m, 4H), 3.69-3.78 (m, 1H), 3.87 (s, 4H), 4.08-4.32 (m, 2H), 6.73 (d, 1H), 6.77-6.89 (m, 1H), 7.06-7.33 (m, 6H). m/s: 295.

Example 4

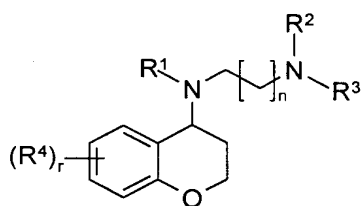
(S)-Chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]methylamine

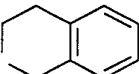
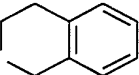
The tan oil from step (d) of Example 3 (1.33 g, 4.52×10^{-3} mole) and triethylamine
15 (1.5 mL, 1.08×10^{-2} mole) were combined in THF (35 mL) and treated with ethyl chloroformate (0.475 mL, 4.97×10^{-3} mole) at ambient temperature. The mixture was stirred for one hour. The reaction mixture was evaporated and the residue was partitioned between water and ethyl acetate. The aqueous portion was extracted with additional ethyl acetate. The combined organic portions were washed (water, brine), dried, and evaporated to a brown oil
20 which was purified by chromatography, eluting with 2:1 ethyl acetate/ hexane (v/v), to give the carbamate as a tan oil (1.49 g, 90%). A solution of the oil in THF (30 mL) was treated with lithium aluminum hydride (0.627 g, 1.65×10^{-2} mole) and refluxed for two hours. The reaction mixture was quenched with sodium sulfate decahydrate until effervescence ceased. Additional THF and diethyl ether were added to aid stirring. The reaction mixture was
25 filtered through diatomaceous earth and the filtrate was evaporated to a purple oil which was purified by chromatography, eluting with 5% 2.0 M ammonia in methanol: 95% DCM (v/v), to give the title compound as a tan oil (1.03 g, 82%). ^1H NMR (DMSO): 1.84-2.02 (m, 2H), 2.24 (s, 3H), 2.53-2.66 (m, 2H), 2.71-2.92 (m, 2H), 3.83 (s, 4H), 3.95-4.14 (m, 2H), 4.26-4.36 (m, 1H), 6.72 (d, 1H), 6.80-6.90 (m, 1H), 7.03-7.26 (m, 5H), 7.47 (d, 1H). m/s: 309.

Examples 5-10

Using an analogous procedure to that described in Example 3(d), the following compounds were prepared.

-27-



| Ex | R ¹ | R ² | R ³ | (R ⁴) _r | n | m/s |
|-----------------|----------------|---|---------------------|--------------------------------|---|-----|
| 5 | Me | Me | -CH ₂ Ph | H | 1 | 311 |
| 6 ¹ | Me |  | | H | 1 | 323 |
| 7 ¹ | Me | -CH ₂ (CH ₂) ₂ CH ₂ - | | H | 1 | 261 |
| 8 ¹ | H | -CH ₂ (CH ₂) ₄ CH ₂ - | | H | 1 | 275 |
| 9 ¹ | H | Me | -CH ₂ Ph | H | 1 | 297 |
| 10 ¹ | H |  | | H | 1 | 309 |

¹ S Enantiomer

NMR (DMSO) results:

5 Example 5: (*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N,N'*-dimethylethane-1,2-diamine, 1.80-1.97 (m, 2H), 2.10 (s, 3H), 2.16 (s, 3H), 2.42-2.59 (m, 4H), 3.46 (s, 2H), 3.91-4.11 (m, 2H), 4.23-4.34 (m, 1H), 6.67-6.73 (m, 1H), 6.80-6.87 (m, 1H), 7.02-7.13 (m, 1H), 7.19-7.35 (m, 5H), 7.40-7.45 (m, 1H).

Example 6: (*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]methylamine, 1.82-2.01 (m, 2H), 2.23 (s, 3H), 2.52-2.83 (m, 8H), 3.54 (s, 2H), 3.93-4.12 (m, 2H), 4.25-4.35 (m, 1H), 6.71 (d, 1H), 6.80-6.90 (m, 1H), 6.95-7.14 (m, 5H), 7.46 (d, 1H).

Example 7: (*S*)-chroman-4-ylmethyl-(2-pyrrolidin-1-ylethyl)amine, 1.56-1.68 (m, 4H), 1.80-2.00 (m, 2H), 2.19 (s, 3H), 2.31-2.60 (m, 8H), 3.91-4.11 (m, 2H), 4.23-4.35 (s, 1H), 6.68 (d, 1H), 6.80-6.91 (m, 1H), 7.02-7.15 (m, 1H), 7.44 (d, 1H).

15 Example 8: (*S*)-(2-azepan-1-ylethyl)chroman-4-ylamine, 1.46-1.63 (m, 8H), 1.83-2.00 (m, 3H), 2.48-2.79 (m, 8H), 3.63-3.72 (m, 1H), 4.07-4.28 (m, 2H), 6.73 (d, 1H), 6.79-6.89 (m, 1H), 7.06-7.16 (m, 1H), 7.22 (d, 1H).

Example 9: (*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N*-methylethane-1,2-diamine, 1.84-1.94 (m, 3H), 2.13 (s, 3H), 2.42-2.55 (m, 2H), 2.63-2.85 (m, 2H), 3.40-3.56 (m, 2H), 3.63-3.72 (m, 1H), 4.07-4.30 (m, 2H), 6.73 (d, 1H), 6.80-6.87 (m, 1H), 7.06-7.17 (m, 1H), 7.19-7.37 (m, 6H).

Example 10: (*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]amine, 1.81-2.12

5 (m, 3H), 2.53-2.92 (m, 8H), 3.57 (s, 2H), 3.68-3.78 (m, 1H), 4.07-4.29 (m, 2H), 6.72 (d, 1H), 6.77-6.85 (m, 1H), 7.00-7.17 (m, 5H), 7.24 (d, 1H).

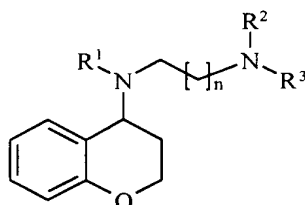
Example 11

***N*-chroman-4-yl-*N,N',N'*-trimethylpropane-1,3-diamine**

4-Chlorochroman (Method A) (0.430 g, 2.30 x 10⁻³ mole) and *N,N,N'*-trimethyl-1,3-propanediamine (0.710 g, 6.11 x 10⁻³ mole) were combined in acetonitrile (25 mL) and heated
10 at 50 °C for 22 hours. The reaction mixture was evaporated and partitioned between 1M sodium hydroxide and diethyl ether. The aqueous portion was extracted with additional diethyl ether. The combined organic portion were washed (water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1%
15 NH₄OH:10% MeOH:89% DCM (v/v/v), to give the product as a colourless oil (0.314 g, 55%).
NMR: 1.47-1.65 (m, 2H), 1.82-1.96 (m, 2H), 2.08 (s, 6H), 2.13 (s, 3H), 2.13-2.49 (m, 4H), 3.94 (t, 1H), 4.00-4.13 (m, 1H), 4.23-4.44 (m, 1H), 6.68 (d, 1H), 6.83 (t, 1H), 7.05 (t, 1H), 7.40 (d, 1H).

Examples 12-20

20 Using an analogous procedure to that described in Examples 1 or 2, the following compounds were prepared.



| <u>Ex</u> | <u>R¹</u> | <u>R²</u> | <u>R³</u> | <u>n</u> | <u>By</u> <u>Ex</u> | <u>m/s</u> | <u>SM</u> |
|-----------|----------------------|---|----------------------|----------|------------------------|------------------|-----------|
| 12 | H | Me | Ph | 2 | 1 | 319 M+2 3 | |
| 13 | H | Me | Me | 1 | 1 | 221 | |
| 14 | H | -(CH ₂) ₂ O(CH ₂) ₂ - | | 1 | 1 | 263 | |
| 15 | H | -(CH ₂) ₂ O(CH ₂) ₂ - | | 2 | 1 | 277 | |
| 16 | H | H | CH ₂ Ph | 1 | 1 | M+2 3=30 5 | |
| 17 | H | -(CH ₂) ₅ - | | 2 | 1 | 275 | |
| 18 | H | -(CH ₂) ₄ - | | 2 | 1 | 261 | |
| 19 | H | -(CH ₂) ₄ - | | 1 | 1 | 247 | |
| 20 | Me | Me | Me | 1 | 2 | 235 | Ex 12 |

NMR results:

- 5 Example 12: *N'*-chroman-4-yl-*N*-methyl-*N*-phenylpropane-1,3-diamine, 1.58-1.75 (m, 2H), 1.80-2.00 (m, 3H), 2.45-2.77 (m, 2H), 2.86 (s, 3H), 3.27-3.50 (m, 2H), 3.65 (s, 1H), 4.07-4.30 (m, 2H), 6.57 (t, 1H), 6.64-6.77 (m, 3H), 6.83 (t, 1H), 7.05-7.20 (m, 3H), 7.26-7.33 (m, 1H).
- Example 13: *N'*-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine, 1.70-2.00 (m, 3H), 2.14 (s, 6H), 2.33 (t, 2H), 2.55-2.78 (m, 2H), 3.68 (t, 1H), 4.06-4.30 (m, 2H), 6.67-6.90 (m, 2H), 7.04-
- 10 7.27 (m, 2H).
- Example 14: chroman-4-yl-(2-morpholin-4-ylethyl)amine, 1.75-1.95 (m, 3H), 2.27-2.47 (m, 6H), 2.60-2.81 (m, 2H), 3.56 (t, 4H), 3.69 (t, 1H), 4.07-4.30 (m, 2H), 6.73 (d, 1H), 6.84 (t, 1H), 7.11 (t, 1H), 7.25 (d, 1H).

Example 15: chroman-4-yl-(3-morpholin-4-ylpropyl)amine, 1.47-1.68 (m, 2H), 1.82-2.00 (m, 3H), 2.23-2.43 (m, 6H), 2.50-2.76 (m, 2H), 3.54 (t, 4H), 3.66 (t, 1H), 4.06-4.30 (m, 2H), 6.72 (d, 1H), 6.83 (t, 1H), 7.10 (t, 1H), 7.27 (d, 1H).

Example 16: *N*-benzyl-*N'*-chroman-4-ylethane-1,2-diamine, 1.83-1.91 (m, 2H), 1.94-2.20 (m, 2H), 2.52-2.90 (m, 4H), 3.61-3.73 (m, 3H), 4.06-4.30 (m, 2H), 6.72 (d, 1H), 6.83 (t, 1H), 7.10 (t, 1H), 7.17-7.40 (m, 6H).

Example 17: chroman-4-yl-(3-piperidin-1-ylpropyl)amine, 1.23-1.67 (m, 8H), 1.80-2.02 (m, 3H), 2.17-2.40 (m, 6H), 2.50-2.73 (m, 2H), 3.65 (t, 1H), 4.07-4.32 (m, 2H), 6.71 (d, 1H), 7.09 (t, 1H), 7.26 (d, 1H).

10 Example 18: chroman-4-yl-(3-pyrrolidin-1-ylpropyl)amine, 1.51-2.00 (m, 10H), 2.30-2.80 (m, 7H), 3.62-3.72 (m, 1H), 4.07-4.32 (m, 2H), 6.71 (d, 1H), 6.83 (t, 1H), 7.10 (t, 1H), 7.26 (d, 1H).

Example 19: chroman-4-yl-(2-pyrrolidin-1-ylethyl)amine, 1.60-1.77 (m, 4H), 1.80-2.00 (m, 3H), 2.34-2.57 (m, 6H), 2.60-2.82 (m, 2H), 3.69 (t, 1H), 4.07-4.31 (m, 2H), 6.72 (d, 1H), 6.84 (t, 1H), 7.11 (t, 1H), 7.24 (d, 1H).

Example 20: *N'*-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine, 1.82-2.00 (m, 2H), 2.10 (s, 6H), 2.16 (s, 3H), 2.23-2.56 (m, 4H), 3.90-4.12 (m, 2H), 4.24-4.37 (m, 1H), 6.68 (d, 1H), 6.83 (t, 1H), 7.08 (t, 1H), 7.43 (d, 1H).

Example 21

20 Chroman-4-yl-(*N*-methyl-2-piperidin-1-ylethyl)amine bismaleate salt

A solution of chroman-4-yl-(*N*-methyl-2-piperidin-1-ylethyl)amine (Example 2) (0.170 g, 6.19×10^{-4} mole) in diethyl ether (20 mL) was treated with a solution of maleic acid (0.177 g, 1.52×10^{-3} mole) in diethyl ether (20 mL). The salt form immediately precipitated, adhering to the sides of the flask as a gum. After solidification upon standing overnight, the material was scraped from the sides of the flask, broken up, and collected by vacuum filtration. The solid was vacuum dried at 50 °C for 24 hours to give the salt as a white solid (0.277 g, 88%). NMR: 1.47-1.60 (m, 2H), 1.66-1.84 (m, 4H), 1.91-2.02 (m, 2H), 2.18 (s, 3H), 2.65-2.90 (m, 2H), 3.05-3.34 (m, 6H), 4.00-4.13 (m, 2H), 4.25-4.35 (m, 1H), 6.14 (s, 4H), 6.75 (d, 1H), 6.89 (t, 1H), 7.13 (t, 1H), 7.46 (d, 1H). m/s: 275.

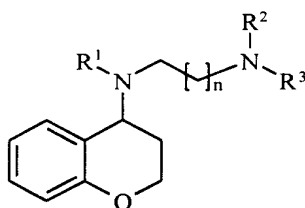
30 Example 22

4-[3-(*N,N*-Dimethylamino)propyl(*N*-methyl)amino]chroman dihydrochloride

4-[3-(*N,N*-Dimethylamino)propyl(*N*-methyl)amino]chroman (0.314 g, 1.26×10^{-3} mole) was dissolved in diethyl ether and treated with an excess of ethereal hydrochloric acid solution. The resulting solid was collected by vacuum filtration under a cloud of nitrogen and vacuum dried at ambient temperature for 20 hours to give the salt as a white solid (0.287 g, 71%). NMR: 2.08-2.48 (m, 4H), 2.62-3.01 (m, 10H), 3.08-3.40 (m, 3H), 4.11-4.20 (m, 1H), 4.32-4.48 (m, 1H), 4.75-4.88 (m, 0.5H), 4.92-5.05 (m, 0.5H), 6.90 (d, 1H), 7.00 (t, 1H), 7.25-7.39 (m, 1H), 7.94-8.08 (m, 1H), 10.51-10.80 (m, 1H), 10.92-11.23 (m, 1H). m/s: 249.

Examples 23-25

Using the procedure of Example 21, salts of the Examples were prepared. The following salts are provided by way of illustration.



Bismaleate

| Ex | R ¹ | R ² | R ³ | n | By Ex | m/s |
|----|----------------|------------------------------------|--------------------|---|-------|-----|
| 23 | H | H | CH ₂ Ph | 1 | 21 | 283 |
| 24 | H | -(CH ₂) ₄ - | | 2 | 21 | 261 |
| 25 | Me | -(CH ₂) ₄ - | | 1 | 21 | 261 |

NMR results:

Example 23: 2.00-2.20 (m, 2H), 3.02-3.24 (m, 5H), 4.09-4.33 (m, 6H), 6.09 (s, 4H), 6.83 (d, 1H), 6.94 (t, 1H), 7.24 (t, 1H), 7.35-7.58 (m, 6H).

Example 24: 1.80-2.30 (m, 8H), 2.89-3.60 (m, 9H, H₂O), 4.27 (t, 2H), 4.42 (s, 1H), 6.04 (s, 4H), 6.89 (d, 1H), 6.99 (t, 1H), 7.31 (t, 1H), 7.42 (d, 1H).

Example 25: 1.85-2.02 (m, 7H), 2.16 (s, 3H), 2.65-2.87 (m, 2H), 3.15-3.43 (m, 5H, H₂O), 4.00-4.13 (m, 2H), 4.25-4.37 (m, 1H), 6.15 (s, 4H), 6.74 (d, 1H), 6.90 (t, 1H), 7.13 (t, 1H), 7.56 (d, 1H).

Example 26

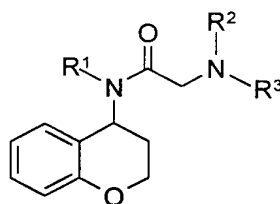
(S)-2-(Benzylmethylamino)-N-chroman-4-ylacetamide

The white solid from Method C (see below) (1.01 g , 4.48×10^{-3} mole) and *N*-benzylmethylamine (1.46 g , 1.20×10^{-2} mole) were combined in acetonitrile (29 mL) and

refluxed for two hours. The reaction mixture was partitioned between water and ethyl acetate. The aqueous portion was extracted with additional ethyl acetate. The combined extracts were washed (water, brine), dried, and evaporated to yield a residue which was purified by chromatography, eluting with 3% 2.0 M ammonia in methanol: 97% DCM (v/v), to give the title compound as an off-white solid (1.25 g, 90%). ¹H NMR (DMSO): 1.88-2.08 (m, 2H), 2.20 (s, 3H), 3.05 (s, 2H), 3.59 (s, 2H), 4.13-4.25 (m, 2H), 5.00-5.11 (m, 1H), 6.78 (d, 1H), 6.82-6.91 (m, 1H), 7.07-7.37 (m, 7H), 8.18 (d, 1H). m/s: 311.

Examples 27-31

Using an analogous procedure to that described in Example 26, the following compounds were prepared.



| Ex | R ¹ | R ² | R ³ | m/s | SM |
|-----------------|----------------|--|---------------------|-----|----|
| 27 ¹ | Me | Me | -CH ₂ Ph | 325 | MB |
| 28 ¹ | Me | | | 337 | MB |
| 29 ¹ | Me | -CH ₂ (CH ₂) ₂ CH ₂ - | | 275 | MB |
| 30 ¹ | H | -CH ₂ (CH ₂) ₄ CH ₂ - | | 289 | MC |
| 31 ¹ | H | | | 323 | MC |

¹ S Enantiomer

SM - Starting Material, MB - Method B, MC - Method C

NMR (DMSO) results:

- 15 Example 27: (*S*)-2-(benzylmethylamino)-*N*-chroman-4-yl-*N*-methylacetamide, 1.81-2.29 (m, 5H), 2.46 (s, 1.3H), 2.70 (s, 1.7H), 3.23-3.43 (m, 2H), 3.46-3.72 (m, 2H), 4.00-4.38 (m, 2H), 5.35-5.44 (m, 0.4H), 5.76-5.86 (m, 0.6H), 6.74-6.96 (m, 3H), 7.08-7.40 (m, 6H).

Example 28: (*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-methyleacetamide, 1.84-2.20 (m, 2H), 2.59-2.97 (m, 6H), 3.26-3.80 (m, 5H), 4.07-4.37 (m, 2H), 5.51-5.61 (m, 0.5H), 5.80-5.89 (m, 0.5H), 6.73-7.20 (m, 8H).

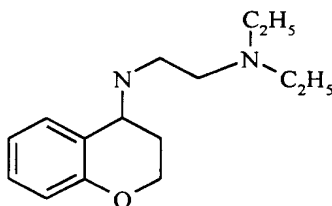
Example 29: (*S*)-*N*-chroman-4-yl-*N*-methyl-2-pyrrolidin-1-ylacetamide, 1.61-1.78 (m, 4H),
5 1.82-2.20 (m, 2H), 2.40-2.64 (m, 5.2H), 2.70 (s, 1.8H), 3.27-3.48 (m, 2H), 4.08-4.37 (m, 2H), 5.43-5.53 (m, 0.4H), 5.74-5.84 (m, 0.6H), 6.75-6.98 (m, 3H), 7.08-7.19 (m, 1H).

Example 30: (*S*)-2-azepan-1-yl-*N*-chroman-4-ylacetamide, 1.43-1.65 (m, 8H), 1.87-2.11 (m, 2H), 2.57-2.70 (m, 4H), 3.12 (s, 2H), 4.11-4.26 (m, 2H), 4.97-5.09 (m, 1H), 6.77 (d, 1H), 6.80-6.93 (m, 1H), 7.07-7.20 (m, 2H), 8.00 (d, 1H).

10 Example 31: (*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)acetamide, 1.90-2.09 (m, 2H), 2.70-2.93 (m, 4H), 3.13-3.24 (m, 2H), 3.67 (s, 2H), 4.13-4.25 (m, 2H), 5.02-5.13 (m, 1H), 6.75 (d, 1H), 6.82-6.92 (m, 1H), 7.00-7.20 (m, 6H), 8.21 (d, 1H).

Reference Example 1

By the procedure of Example 1 the following compound was prepared:



15 NMR results: 0.94 (t, 6H), 1.73-2.00 (m, 3H), 2.30-2.80 (m, 8H), 3.68 (t, 1H), 4.05-4.33 (m, 2H), 6.73 (d, 1H), 6.84 (t, 1H), 7.10 (t, 1H), 7.23 (d, 1H); m/s: 249.

Preparation of Starting Materials

20 The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of the starting materials used in the above reactions.

Method A

4-Chlorochroman

25 4-Chromanol (0.578 g, 3.85×10^{-3} mole) was treated with thionyl chloride (2.0 mL, 2.74×10^{-2} mole) at ambient temperature. After stirring for 48 hours, the reaction mixture was evaporated. The residue was partially purified by chromatography, eluting with 9:1 hexane:ethyl acetate (v/v) to give the title compound as a tan oil (0.430 g, 66%).

Method B**(S)-4-[N-Methyl-2-chloroacetamido]thiochroman**

(S)-N-Methyl-4-aminochroman (3.33 g, 2.04×10^{-2} mole) and 2,6-lutidine (3.6 mL, 3.09×10^{-2} mole) were combined in DCM (45 mL) and cooled to 0 °C (ice/water/sodium chloride). Chloroacetyl chloride (2.0 mL, 2.51×10^{-2} mole) was added dropwise, maintaining the reaction temperature at <10 °C. Upon complete addition, the mixture was stirred cold for one hour. The reaction mixture was partitioned between 1N aqueous hydrochloric acid and DCM. The organic portion was washed with additional 1N aqueous hydrochloric acid. The combined aqueous portions were extracted with DCM. The combined organic portions were washed (saturated aqueous sodium bicarbonate, water, brine), dried, and evaporated to a yellow oil which was purified by chromatography, eluting with 1:1 hexane/ethyl acetate (v/v), to give a yellow oil (4.84 g, 99%). ¹H NMR (DMSO): 1.85-2.20 (m, 2H), 2.46-2.55 (m, 1H), 2.69 (s, 2H), 4.13-4.39 (m, 2H), 4.43-4.64 (m, 2H), 5.23-5.33 (m, 0.3H), 5.72-5.83 (m, 0.7H), 6.76-7.04 (m, 3H), 7.10-7.22(m, 1H). m/s: 240.

Method C**(S)-4-[2-Chloroacetamido]thiochroman**

(S)-4-Aminochroman (3.42 g, 2.29×10^{-2} mole) and 2,6-lutidine (4.0 mL, 3.43×10^{-2} mole) were combined in DCM (48 mL) and cooled to 0 °C (ice/water/sodium chloride). Chloroacetyl chloride (2.0 mL, 2.51×10^{-2} mole) was added dropwise, maintaining the reaction temperature at <5 °C. Upon complete addition, the mixture was stirred cold for one hour. The reaction mixture was partitioned between 1 N aqueous hydrochloric acid and DCM. The organic portion was washed with additional 1N aqueous hydrochloric acid. The combined aqueous portions were extracted with DCM. The combined organic portions were washed (saturated aqueous sodium bicarbonate, water, brine), dried, and evaporated to a solid. The solid was triturated (hexane), collected, and dried to give a white solid (4.86 g, 94%). ¹H NMR (DMSO): 1.82-2.12 (m, 2H), 4.02-4.27 (m, 4H), 4.93-5.04 (m, 1H), 6.79 (d, 1H), 6.84-6.95 (m, 1H), 7.09-7.23 (m, 2H), 8.74 (d, 1H).

Example 32

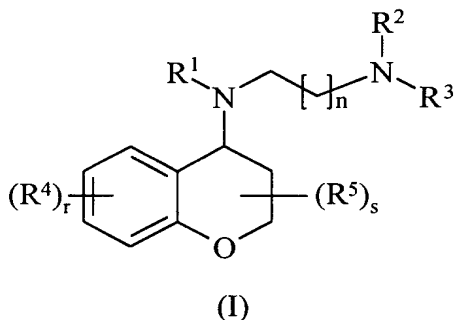
Following conventional procedures well known in the pharmaceutical art the following representative pharmaceutical dosage forms containing a compound of formula (I) can be prepared:

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| | | |
|---|-----------------------------|-------------------|
| (a) <u>Tablet</u> | | <u>mg/tablet</u> |
| Compound of Formula I | | 50.0 |
| Mannitol, USP | | 223.75 |
| Croscarmellose sodium | | 60 |
| 5 | Maize starch | 15.0 |
| Hydroxypropylmethylcellulose (HPMC), USP 2.25 | | |
| Magnesium stearate | | 3.0 |
| (b) <u>Capsule</u> | | <u>mg/capsule</u> |
| Compound of Formula I | | 10.0 |
| 10 | Mannitol, USP | 488.5 |
| Croscarmellose sodium | | 15.0 |
| Magnesium stearate | | 1.5 |
| (c) <u>Injection</u> | | |
| For intravenous administration, a compound of Formula I is dissolved in an isotonic | | |
| 15 | sterile solution (5 mg/mL). | |

CLAIMS:

1. A method of treating neurological disorders comprising administration of a therapeutically-effective amount of any compound according to formula (I):



wherein:

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

- R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring, wherein said C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6} alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, N - C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkoxycarbonyl, N - C_{1-6} alkylcarbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl or phenyl C_{1-6} alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally

substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, *N*-(C₁₋₆alkyl)amino, *N,N*-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, *N*-(C₁₋₆alkyl)carbamoyl, *N,N*-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0, 1 or 2, C₁₋₆alkoxycarbonyl, *N*-(C₁₋₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl or phenylC₁₋₆alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkanoyl or C₁₋₆alkylsulphonyl;

R⁴ at each occurrence is selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkyl, cyano, nitro or C₂₋₆alkenyl;

R⁵ is C₁₋₆alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R⁴ may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the value of R⁵ may be the same or different;

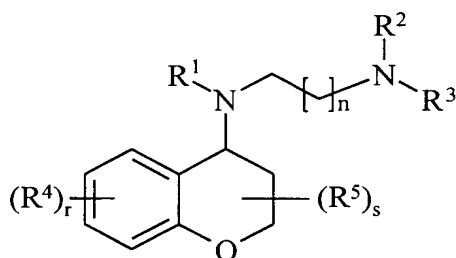
or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

2. The method according to Claim 1, for treating stroke, head trauma, transient cerebral ischaemic attack, and chronic neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, diabetic neuropathy, amyotrophic lateral sclerosis, multiple sclerosis and AIDS-related dementia.

3. The method according to Claim 1, for treating neurological disorders treatable by inhibition of the the [³H]-emopamil binding site.

4. A pharmaceutical composition comprising any compound according to formula (I), or a *in vivo*-hydrolysable ester, amide or carbamate thereof, together with a pharmaceutically-acceptable carrier, wherein, in a compound of formula (I):

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(I)

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring, wherein said C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6} alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, N - C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkoxycarbonyl, N - C_{1-6} alkylcarbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl or phenyl C_{1-6} alkyl; or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with

- 5 C_{1-6} alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring, wherein said C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6} alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, N - C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkoxycarbonyl, N - C_{1-6} alkylcarbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with
- 10 N,N -(C_{1-6} alkyl) $_2$ carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl, heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with
- 15 sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with
- 20 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkanoyl, C_{1-6} alkylsulphonyl or phenyl C_{1-6} alkyl;

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a

heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto,

- 25 sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with

₆alkyl)sulphamoyl, *N,N*-(C₁₋₆alkyl)₂sulphamoyl or phenylC₁₋₆alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkanoyl or C₁₋₆alkylsulphonyl;

- R⁴ at each occurrence is selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkyl, cyano, nitro or C₂₋₆alkenyl;
- R⁵ is C₁₋₆alkyl;
- n is 1 or 2;
- r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R⁴ may be the same or different; and
- s is 0, 1, 2 or 3 wherein at each occurrence the value of R⁵ may be the same or different;
- or a pharmaceutically-acceptable salt thereof.

5. A pharmaceutical composition according to Claim 4, comprising any compound in accord with formula (I), wherein:
- R¹ is hydrogen or C₁₋₆alkyl;
- R² and R³ are independently selected from hydrogen, aryl and C₁₋₆alkyl optionally substituted with aryl;
- or R² and R³ and the nitrogen atom to which they are attached in combination form a heterocyclic ring;
- r is 0;
- s is 0;
- n is 1 or 2.

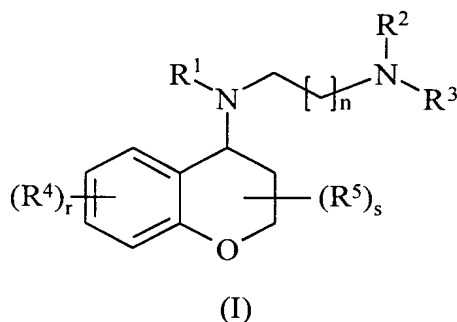
6. A pharmaceutical composition according to Claim 6, comprising any compound in accord with formula (I), wherein:
- R¹ is hydrogen or methyl;
- R² and R³ are independently selected from methyl, ethyl or benzyl,
- or R² and R³ and the nitrogen atom to which they are attached in combination form a ring selected from pyrrolidin-1-yl, piperidin-1-yl and morpholino.

7. A pharmaceutical composition according to Claim 6, comprising any compound in accord with formula (I), wherein:

R^2 and R^3 are independently selected from methyl or benzyl,

or R^2 and R^3 and the nitrogen atom to which they are attached in combination form a
5 ring selected from pyrrolidin-1-yl and piperidin-1-yl.

8. Any compound according to formula (I):



10 wherein:

R^1 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring, wherein said C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl are
15 optionally substituted with one or more groups selected from halo, nitro, hydroxy, C_{1-6} alkoxy, cyano, amino, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, mercapto, sulphamoyl, mesyl, N - C_{1-6} alkylamino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkoxycarbonyl, N - C_{1-6} alkylcarbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, aryl, a carbon linked heteroaryl, a carbon-linked heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring; and wherein any aryl, heteroaryl,
20 heterocycle, C_{3-12} cycloalkyl and C_{3-12} cycloalkyl fused to a benzene ring may be optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkanoyloxy, N -(C_{1-6} alkyl)amino, N,N -(C_{1-6} alkyl) $_2$ amino, C_{1-6} alkanoylamino, N -(C_{1-6} alkyl)carbamoyl, N,N -(C_{1-6} alkyl) $_2$ carbamoyl, C_{1-6} alkylS(O) $_a$ wherein a is 0, 1 or 2, C_{1-6} alkoxycarbonyl, N -(C_{1-6} alkyl)sulphamoyl, N,N -(C_{1-6} alkyl) $_2$ sulphamoyl and phenyl C_{1-6} alkyl; and a heterocycle or a
25

heteroaryl ring containing an -NH- group may be optionally substituted on this nitrogen with C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkanoyl, C₁₋₆alkylsulphonyl or phenylC₁₋₆alkyl;

or R² and R³ and the nitrogen atom to which they are attached in combination form a heterocyclic or heteroaryl ring and wherein said heterocyclic or heteroaryl ring is optionally substituted on a ring carbon with one or more groups selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkanoyl, C₁₋₆alkanoyloxy, N-(C₁₋₆alkyl)amino, N,N-(C₁₋₆alkyl)₂amino, C₁₋₆alkanoylamino, N-(C₁₋₆alkyl)carbamoyl, N,N-(C₁₋₆alkyl)₂carbamoyl, C₁₋₆alkylS(O)_a wherein a is 0, 1 or 2, C₁₋₆alkoxycarbonyl, N-(C₁₋₆alkyl)sulphamoyl, N,N-(C₁₋₆alkyl)₂sulphamoyl or phenylC₁₋₆alkyl; and a heterocyclic or a heteroaryl ring containing an -NH- group is optionally substituted on this nitrogen with C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkanoyl or C₁₋₆alkylsulphonyl;

R⁴ at each occurrence is selected from halo, hydroxy, C₁₋₆alkyl, C₁₋₆alkoxy, haloC₁₋₆alkyl, cyano, nitro or C₂₋₆alkenyl;

R⁵ is C₁₋₆alkyl;

n is 1 or 2;

r is 0, 1, 2, 3 or 4, wherein at each occurrence the value of R⁴ may be the same or different; and

s is 0, 1, 2 or 3 wherein at each occurrence the value of R⁵ may be the same or different;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof;

with a proviso wherein in such compounds:

if r is 1, R⁴ is a 6-linked cyano moiety, s is 2 and both R⁵ moieties are 2-linked methyl, n is 1, and R¹ and R² are both H, then R³ is not phenyl or benzyl;

if r and s are both 0, R¹ is H and n is 2, then R¹ and R² are not both ethyl or not both H, or

if r and s are both 0, R¹ is H and n is 1, then R¹ and R² are not both ethyl.

9. A compound according to Claim 8, wherein:

R¹ is hydrogen or C₁₋₆alkyl;

R² and R³ are independently selected from hydrogen, aryl and C₁₋₆alkyl optionally substituted with aryl;

or R² and R³ and the nitrogen atom to which they are attached in combination form a heterocyclic ring;

r is 0;

s is 0;

5 n is 1 or 2;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

10. A compound according to Claim 9, wherein:

10 R¹ is hydrogen or methyl;

R² and R³ are independently selected from methyl, ethyl or benzyl,

or R² and R³ and the nitrogen atom to which they are attached in combination form a ring selected from pyrrolidin-1-yl, piperidin-1-yl and morpholino;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate

15 thereof.

11 A compound according to Claim 10, wherein:

R² and R³ are independently selected from methyl or benzyl,

or R² and R³ and the nitrogen atom to which they are attached in combination form a
20 ring selected from pyrrolidin-1-yl and piperidin-1-yl;

or a pharmaceutically-acceptable salt or an *in vivo*-hydrolysable ester, amide or carbamate thereof.

12. A compound according to Claim 8, selected from:

25 chroman-4-yl-(2-piperidin-1-ylethyl)amine;

chroman-4-yl-(*N*-methyl-2-piperidin-1-ylethyl)amine;

(*S*)-chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]amine;

(*S*)-chroman-4-yl-[2-(1,3-dihydroisoindol-2-yl)ethyl]methanamine

(*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N,N'*-dimethylethane-1,2-diamine;

30 (*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]methanamine;

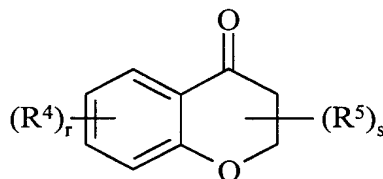
(*S*)-chroman-4-ylmethyl-(2-pyrrolidin-1-ylethyl)amine;

- (*S*)-(2-azepan-1-ylethyl)chroman-4-ylamine;
 (*S*)-*N*-benzyl-*N'*-chroman-4-yl-*N*-methylethane-1,2-diamine;
 (*S*)-chroman-4-yl-[2-(3,4-dihydro-1*H*-isoquinolin-2-yl)ethyl]amine;
N-chroman-4-yl-*N,N',N'*-trimethylpropane-1,3-diamine;
 5 *N'*-chroman-4-yl-*N*-methyl-*N*-phenylpropane-1,3-diamine;
N'-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine;
 chroman-4-yl-(2-morpholin-4-ylethyl)amine;
 chroman-4-yl-(3-morpholin-4-ylpropyl)amine;
N-benzyl-*N'*-chroman-4-ylethane-1,2-diamine;
 10 chroman-4-yl-(3-piperidin-1-ylpropyl)amine;
 chroman-4-yl-(3-pyrrolidin-1-ylpropyl)amine;
 chroman-4-yl-(2-pyrrolidin-1-ylethyl)amine;
N'-chroman-4-yl-*N,N*-dimethylethane-1,2-diamine;
 (*S*)-2-(benzylmethylamino)-*N*-chroman-4-ylacetamide;
 15 (*S*)-2-(benzylmethylamino)-*N*-chroman-4-yl-*N*-methylacetamide;
 (*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-methylacetamide;
 (*S*)-*N*-chroman-4-yl-*N*-methyl-2-pyrrolidin-1-ylacetamide;
 (*S*)-2-azepan-1-yl-*N*-chroman-4-ylacetamide, and
 (*S*)-*N*-chroman-4-yl-2-(3,4-dihydro-1*H*-isoquinolin-2-yl)acetamide.

20

13. A method of making a compound of formula (I) according to Claim 8, wherein R^1 , R^2 , R^3 , R^4 , R^5 , s , r and n unless otherwise defined are as defined in Claim 8, said method comprising:

a) reacting a ketone of formula (II):

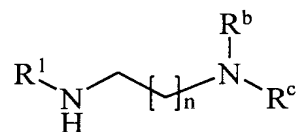


(II)

25

with an amine of formula (III):

-44-



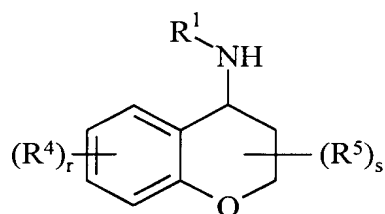
(III);

wherein R^b and R^c are R^2 and R^3 respectively, unless the value of R^2 and/or R^3 is hydrogen, in which case the appropriate R^b and/or R^c is a suitable amino protecting group such as those

5 defined below;

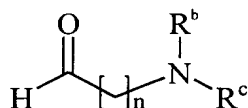
or

b) reacting an amine of formula (IV):



(IV)

10 with an aldehyde of formula (V):

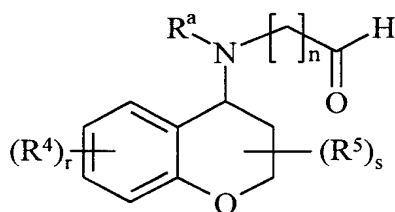


(V)

wherein R^b and R^c are as defined above;

or

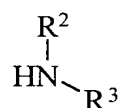
15 c) reacting an aldehyde of formula (VI):



(VI)

with an amine of formula:

-45-

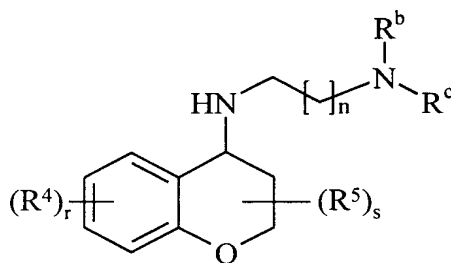


(VII)

wherein R^a is R^1 unless the value of R^1 is hydrogen, in which case R^a is a suitable amino protecting group such as those defined below;

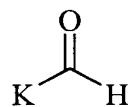
5 or

d) if R^1 is C_{1-6} alkyl, reacting a compound of formula (VIII):



(VIII)

wherein R^b and R^c are as defined above, with a compound of formula (IX);

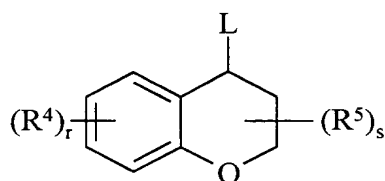


(IX)

wherein K is hydrogen or C_{1-5} alkyl;

or

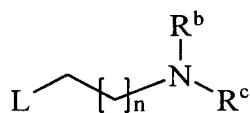
e) reacting a compound of formula (X):



(X)

wherein L is a suitable displaceable group, with an amine of formula (III); or

f) reacting an amine of formula (IV) with a compound of formula (XI):



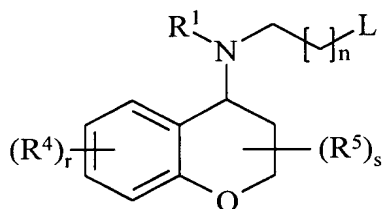
-46-

(XI)

wherein L is a suitable displaceable group and R^b and R^c are as defined above;

or

g) reacting a compound of formula (XII):



(XII)

wherein L is a suitable displaceable group, with an amine of formula (VII);

or

h) if R¹ is not hydrogen, reacting a compound of formula (VIII) with a compound of

10 formula (XIII):

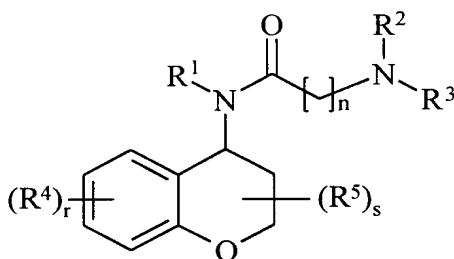
R¹-L

(XIII)

wherein L is a suitable displaceable group;

or

15 i) reducing a compound of formula (XIV):

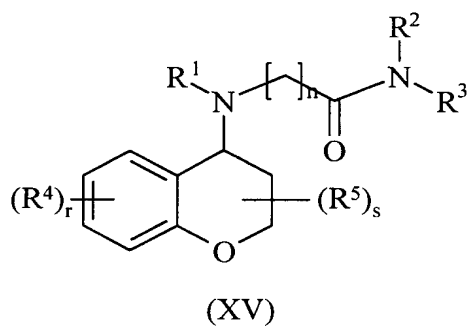


(XIV)

or

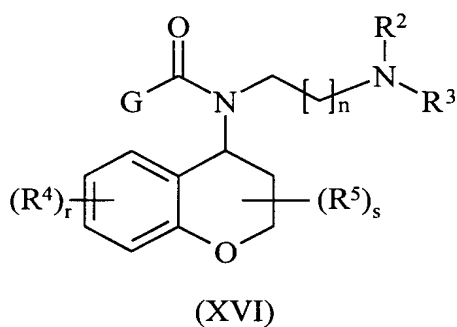
j) reducing a compound of formula (XV):

-47-



or

k) if R^1 is not hydrogen, reducing a compound of formula (XVI):



where:

for preparing a compound wherein R^1 is methyl, G is a suitable displaceable group;

or

10 for preparing a compound wherein R^1 is C_{2-6} alkyl, G is C_{1-5} alkyl;

and thereafter if necessary:

converting a compound of the formula (I) into another compound of the formula (I);

removing any protecting groups; or

forming a pharmaceutically-acceptable salt or *in vivo*-hydrolysable ester, amide or

15 carbamate.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02304

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D311/68 C07D405/12 A61K31/353 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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A document defining the general state of the art which is not considered to be of particular relevance

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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& document member of the same patent family

Date of the actual completion of the international search

16 November 2000

Date of mailing of the international search report

01/12/2000

Name and mailing address of the ISA

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Beslier, L

INTERNATIONAL SEARCH REPORT

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Intern. Patent Application No

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| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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Information on patent family members

International Application No

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